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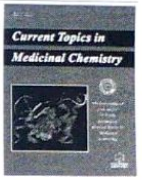
REVIEW ARTICLE



Structural-activity Relationship of Metallo-aminoquines as Next Generation Antimalarials

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Abstract: Apicomplexian parasite of the genus *Plasmodium* is the causative agent of malaria, one of the most devastating, furious and common infectious disease throughout the world. According to the latest World malaria report, there were 229 million cases of malaria in 2019 majorly consist of children under 5 years of age. Some of known analogues *viz.* quinine, quinoline-containing compounds have been used for last century in the clinical treatment of malaria. Past few decades witnessed the emergence of multi-drug resistance (MDR) strains of *Plasmodium* species to existing antimalarials pressing the need for new drug candidates. Thus, in those decades bioorganometallic approach to malaria therapy has been introduced which led to the discovery of noval metalcontaining aminoquinolines analogues *viz.* ferroquine (FQ or **1**), Ruthenoquine (RQ or **2**) and other related potent metal-analogues. It observed that some metal containing analogues (Fe-, Rh-, Ru-, Re-, Au-, Zn-, Cr-, Pd-, Sn-, Cd-, Ir-, Co-, Cu-, and Mn-aminoquines) were more potent; however, some were equally potent as Chloroquine (CQ) and **1**. This is probably due to the intertion of metals in the CQ *via* various approaches, which might be a very attractive strategy to develop a SAR of novel metal containing antimalarials. Thus, this review aim to summarize the SAR of metal containing aminoquines towards the discovery of potent antimalarial hybrids to provide an insight for rational designs of more effective and less toxic metal containing amonoquines.

Keywords: Chloroquine, Ferroquine, Aminoquinolines, Antimalarial, *In vitro*, *In vivo*, Cytotoxicity, β-Hematin inhibition.

1. INTRODUCTION

Bio-organometallic chemistry has now emerged as a rapidly evolving area that connects classical organometallic chemistry to applied biology, medicine and molecular biotechnology [1]. These compounds have played a key role in biology and medicine for last few decades, even though they are better known for catalysis and other applications [2, 3]. Replacement of organic moieties with organometallics has resulted in metallo-pharmaceuticals with potential advantages such as stability, potential drug like predictability, and the capability to tune ligand affinities with efficient biological targetings [4]. The use of these analogues in medicinal chemistry has recently increased as they have the ability to modulate pharmacokinetic or pharmacodynamic profile of drugs [5, 6].

For the last few decades, malaria parasite has developed resistance against the available known drugs (*viz.* CQ, AMQ, FQ, Artemisinin *etc.*); thus, resulting in increased severity of the situation [7-10]. A variety of synthetic aminoquinoline based drugs were used to treat malaria since 1950s. Among the most successful drugs viz. quinine, chloroquine (CQ), mefloquine (MFQ), amodiaquine (AMQ), and Artemisinin (Art), *etc.* were also resistant towards malaria parasite; however, they were useful in the defense mechanism where they converted toxic heme into a non-toxic polymer form (hemazoin) in the food vacuole [11-13]. Some drugs do not exhibit antimlarial activity; however, most of the drugs are either insoluble or lipophilic. It was observed that direct relation between lipophilicity and antiplasmodial activity supports direct intracellular iron-chelation as the mode of action: the higher the affinity to cross the lipid membranes, the higher is the antimalarial activity [14].

A number of transition metal ions led to coordination complexes with CQ [15-18], which have been shown to exhibit improved efficacy in both CQ^S and CQ^R strains of *P. falciparum*, compared to the parent drug; however, the mechanism of action associated with the metal-based antimalarials is still under study. It observed that the presence of the metal ion led to an enhanced activity.

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